

## WEST Search History

DATE: Friday, January 09, 2004

<u>Hide?</u>	<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>
<i>DB=USPT; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i>			
<input type="checkbox"/>	L5	L4 and VEGF	165
<input type="checkbox"/>	L4	L3 and chimeric adj antibody	165
<input type="checkbox"/>	L3	L2	933
<i>DB=PGPB,USPT,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i>			
<input type="checkbox"/>	L2	L1 and angiogenesis	3801
<input type="checkbox"/>	L1	VEGF and antibody	5277

END OF SEARCH HISTORY

=> scFVs  
L1 291 SCFVS

=> L1 and VEGF  
8662 VEGF  
95 VEGFS  
8666 VEGF  
(VEGF OR VEGFS)

L2 3 L1 AND VEGF

=> L1 and gene therapy  
827526 GENE  
311930 GENES  
875641 GENE  
(GENE OR GENES)  
212440 THERAPY  
14097 THERAPIES  
220053 THERAPY  
(THERAPY OR THERAPIES)  
32409 GENE THERAPY  
(GENE (W) THERAPY)

L3 20 L1 AND GENE THERAPY

=> DIS L3 1- IBIB IABS

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NEWS 4 DEC 08 INPADOC: Legal Status data reloaded  
NEWS 5 SEP 29 DISSABS now available on STN  
NEWS 6 OCT 10 PCTFULL: Two new display fields added  
NEWS 7 OCT 21 BIOSIS file reloaded and enhanced  
NEWS 8 OCT 28 BIOSIS file segment of TOXCENTER reloaded and enhanced  
NEWS 9 NOV 24 MSDS-CCOHS file reloaded  
NEWS 10 DEC 08 CABAA reloaded with left truncation  
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NEWS 13 DEC 09 STN Entry Date available for display in REGISTRY and CA/CAplus  
NEWS 14 DEC 17 DGENE: Two new display fields added  
NEWS 15 DEC 18 BIOTECHNO no longer updated  
NEWS 16 DEC 19 CROPU no longer updated; subscriber discount no longer available  
NEWS 17 DEC 22 Additional INPI reactions and pre-1907 documents added to CAS databases  
NEWS 18 DEC 22 IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields  
NEWS 19 DEC 22 ABI-INFORM now available on STN  
  
NEWS EXPRESS DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003  
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FILE COVERS 1907 - 9 Jan 2004 VOL 140 ISS 3  
FILE LAST UPDATED: 8 Jan 2004 (20040108/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> VEGF

8655 VEGF  
95 VEGFS  
L1 8659 VEGF  
(VEGF OR VEGFS)

=> chimeric (w) antibody

37684 CHIMERIC  
24 CHIMERICS  
37693 CHIMERIC  
(CHIMERIC OR CHIMERICS)  
256291 ANTIBODY  
283989 ANTIBODIES  
390476 ANTIBODY  
(ANTIBODY OR ANTIBODIES)

L2 971 CHIMERIC (w) ANTIBODY

=> L1 and L2

L3 14 L1 AND L2

=> treatment and L1

1862991 TREATMENT  
171435 TREATMENTS  
1955694 TREATMENT  
(TREATMENT OR TREATMENTS)

L4 2003 TREATMENT AND L1

=> L4 and L2

L5 3 L4 AND L2

=> DIS L5 1- IBIB IABS

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):Y  
THE ESTIMATED COST FOR THIS REQUEST IS 7.62 U.S. DOLLARS  
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2003:335256 CAPLUS  
DOCUMENT NUMBER: 138:352765

TITLE: Antibody or immunoadhesin having Fc region for diagnosis and treatment of cancer, autoimmune disease, inflammation, or infection  
 INVENTOR(S): Presta, Leonard G.  
 PATENT ASSIGNEE(S): Genentech, Inc., USA  
 SOURCE: PCT Int. Appl., 139 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035835	A2	20030501	WO 2002-US33739	20021022
WO 2003035835	A3	20031016		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003157108	A1	20030821	US 2002-277370	20021022
PRIORITY APPLN. INFO.: US 2001-337642P P 20011025 US 2002-347694P P 20020109				

**ABSTRACT:**  
 The present invention concerns compns. comprising a glycoprotein having an Fc region, wherein about 80-100% of the glycoprotein in the compn. comprises a mature core carbohydrate structure which lacks fucose, attached to the Fc region of the glycoprotein. The preferred glycoprotein is an antibody or immunoadhesin. The antibody or immunoadhesin is a chimeric, humanized or human antibody or immunoadhesin. The antibody or immunoadhesin is specific to B cell surface marker, ErbB receptor, tumor antigen or angiogenic factor, such as CD20, HER2, VEGF, CD40 or prostate stem cell antigen. The antibody or immunoadhesin is useful for treating cancer, autoimmune disease, inflammatory disease, infection, or condition where removal of cells or tissue is desired.

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2001:338563 CAPLUS  
 DOCUMENT NUMBER: 134:348629  
 TITLE: Modulation of eNOS activity using VEGF, a variant, or VEGF receptor agonists and therapeutic uses thereof  
 INVENTOR(S): Shen, Ben-Quan; Zioncheck, Thomas  
 PATENT ASSIGNEE(S): Genentech, Inc., USA  
 SOURCE: PCT Int. Appl., 71 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032695	A2	20010510	WO 2000-US30294	20001102
WO 2001032695	A3	20020214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,  
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 EP 1225910 A2 20020731 EP 2000-980281 20001102  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
 JP 2003513105 T2 20030408 JP 2001-535394 20001102  
 PRIORITY APPLN. INFO.: US 1999-163132P P 19991102  
 WO 2000-US30294 W 20001102

#### ABSTRACT:

The present invention provides uses of VEGF, a variant, or  
 \*\*\*VEGF\*\*\* receptor agonists for the up-regulation of eNOS expression and  
 activity. VEGF, its variants, and VEGF receptor agonists  
 are useful in the treatment of or prevention from hypertension,  
 diabetes, angina, thrombosis, atherosclerosis, heart failure, and other  
 conditions or disorders wherein nitric oxide is an important regulator.  
 Methods of prep. the variants are also disclosed in the patent.

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:911535 CAPLUS  
 DOCUMENT NUMBER: 134:85128  
 TITLE: Diagnostics and remedies for diseases with  
 participation of macrocytes/macrophages  
 INVENTOR(S): Shitara, Kenya; Shibuya, Masabumi  
 PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan  
 SOURCE: PCT Int. Appl., 163 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Japanese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000079275	A1	20001228	WO 2000-JP3957	20000616
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1199565	A1	20020424	EP 2000-937283	20000616
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
PRIORITY APPLN. INFO.:			JP 1999-171709	A 19990617
			WO 2000-JP3957	W 20000616

#### ABSTRACT:

Diagnostics and remedies for inflammatory diseases, delayed hypersensitivity,  
 malignant tumor and arteriosclerosis which contain, as the active ingredient, a  
 substance binding to human VEGF receptor Flt-1 or a substance  
 inhibiting signal transduction mediated by human VEGF receptor Flt-1.  
 The human VEGF receptor Flt-1-binding substance is a monoclonal or  
 polyclonal antibody, chimeric antibody, or antibody  
 fragment.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> DIS L3 1- IBIB IABS

YOU HAVE REQUESTED DATA FROM 14 ANSWERS - CONTINUE? Y/(N):Y  
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L3 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2003:972195 CAPLUS  
DOCUMENT NUMBER: 140:26922  
TITLE: Chimeric/humanized antibodies comprising viral coat protein, peptide tag and linkers for screening target antigen-binding polypeptides as therapeutics and reagents  
INVENTOR(S): Fuh, Germaine G.; Sidhu, Sachdev S.  
PATENT ASSIGNEE(S): Genentech, Inc., USA  
SOURCE: PCT Int. Appl., 205 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003102157	A2	20031211	WO 2003-US17545	20030603
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRIORITY APPLN. INFO.:			US 2002-385338P	P 20020603
			US 2003-463656P	P 20030416

ABSTRACT:

The invention provides comprising variant amino acids in CDRs of antibody variable domains. These polypeptides provide a source of great sequence diversity that can be used as a source for identifying novel antigen binding polypeptides. The target antigen is VEGF, IGF-1 or Her-2. The invention also provides these polypeptides as fusion polypeptides to heterologous polypeptides such as at least a portion of phage or viral coat proteins, tags, and linkers. The viral coat protein consists of protein pIII, major coat protein pVIII, Soc, Hoc, gpD, pV1 or variant; and the peptide tag is gD, c-myc, poly-His, fluorescence protein, or .beta. galactosidase. Libraries comprising a plurality of these polypeptides are also provided. In addn., methods of and compns. for generating and using these polypeptides and libraries are provided.

L3 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2003:863449 CAPLUS  
DOCUMENT NUMBER: 139:336930  
TITLE: Antibodies specific to KDR/Flk-1 phosphorylated at tyrosine 1214, and its uses in drug screening and therapy  
INVENTOR(S): Shibuya, Masashi; Furuya, Akiko; Shitara, Kenya  
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 23 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003310276	A2	20031105	JP 2002-129072	20020430
PRIORITY APPLN. INFO.:			JP 2002-129072	20020430

ABSTRACT:

Antibodies specific to vascular endothelial growth factor receptor KDR/Flk-1 phosphorylated at tyrosine at position 1214 (Y1214), and use in various therapeutic and drug screening applications, are disclosed. Various angiogenesis-related methods using this substance are provided: a method for inhibiting the signal transduction of KDR/Flk-1; a method for inhibiting cell proliferation; a method for inhibiting angiogenesis; a method for screening a cell proliferation inhibitor; a method for screening an angiogenesis inhibitor; a method for screening a substance inhibiting the signal transduction of KDR/Flk-1; a method for judging whether or not a test substance inhibits the signal transduction of KDR/Flk-1; a method for screening a substance inhibiting the phosphorylation at tyrosine at the 1214-position of KDR/Flk-1.

L3 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:656789 CAPLUS

DOCUMENT NUMBER: 139:196277

TITLE: Antibody variants with faster antigen association rates for diagnostics and therapeutic uses

INVENTOR(S): Lowman, Henry B.; Marvin, Jonathan S.

PATENT ASSIGNEE(S): Genentech, Inc., USA

SOURCE: PCT Int. Appl., 81 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068801	A2	20030821	WO 2003-US4184	20030211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003224397	A1	20031204	US 2003-364953	20030211
PRIORITY APPLN. INFO.:			US 2002-355895P	P 20020211
			US 2002-409685P	P 20020910

ABSTRACT:

Antibody variants with higher affinity to antigen are disclosed. The antibody variants have one or more amino acid alteration(s) in or adjacent to at least one hypervariable region thereof which increase charge complementarity between the antibody variant and an antigen to which it binds. Variants of anti-\*\*\*VEGF\*\*\* antibody Y0101, anti-tissue factor antibody D3H44 and anti-HER2 antibody 4D5 were prep'd. and tested.

L3 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2003:335256 CAPLUS  
 DOCUMENT NUMBER: 138:352765  
 TITLE: Antibody or immunoadhesin having Fc region for diagnosis and treatment of cancer, autoimmune disease, inflammation, or infection  
 INVENTOR(S): Presta, Leonard G.  
 PATENT ASSIGNEE(S): Genentech, Inc., USA  
 SOURCE: PCT Int. Appl., 139 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035835	A2	20030501	WO 2002-US33739	20021022
WO 2003035835	A3	20031016		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2003157108	A1	20030821	US 2002-277370	20021022
PRIORITY APPLN. INFO.:			US 2001-337642P	P 20011025
			US 2002-347694P	P 20020109

ABSTRACT:  
 The present invention concerns compns. comprising a glycoprotein having an Fc region, wherein about 80-100% of the glycoprotein in the compn. comprises a mature core carbohydrate structure which lacks fucose, attached to the Fc region of the glycoprotein. The preferred glycoprotein is an antibody or immunoadhesin. The antibody or immunoadhesin is a chimeric, humanized or human antibody or immunoadhesin. The antibody or immunoadhesin is specific to B cell surface marker, ErbB receptor, tumor antigen or angiogenic factor, such as CD20, HER2, VEGF, CD40 or prostate stem cell antigen. The antibody or immunoadhesin is useful for treating cancer, autoimmune disease, inflammatory disease, infection, or condition where removal of cells or tissue is desired.

L3 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2003:273850 CAPLUS  
 DOCUMENT NUMBER: 139:336677  
 TITLE: A Phase I Study of Anti-Kinase Insert Domain-containing Receptor Antibody, IMC-1C11, in Patients with Liver Metastases from Colorectal Carcinoma  
 AUTHOR(S): Posey, James A.; Ng, Thian C.; Yang, Baolian; Khazaeli, M. B.; Carpenter, Mark D.; Fox, Floyd; Needle, Mike; Waksal, Harlan; LoBuglio, Albert F.  
 CORPORATE SOURCE: Comprehensive Cancer Center, Division of Hematology/Oncology, Departments of Medicine and Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, 35294-3300, USA  
 SOURCE: Clinical Cancer Research (2003), 9(4), 1323-1332  
 CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ABSTRACT:

Angiogenesis plays an important role in colorectal cancer progression. Stimulation of vascular endothelial growth factor receptor (VEGFR), a transmembrane glycoprotein, results in endothelial mitogenesis. Within this family of receptors, VEGFR2/kinase-insert-domain-contg. receptor (KDR) appear to be principally up-regulated during tumorigenesis. A chimeric anti-KDR antibody, IMC-1C11, blocks VEGFR-KDR interaction and inhibits VEGFR-induced endothelial cell proliferation. This trial seeks to assess the safety, tolerability and feasibility of targeting an important pathway in tumorigenesis. In a dose-escalation, single-agent study of IMC-1C11, we enrolled 14 patients with colorectal carcinoma and hepatic metastases. Safety-, pharmacokinetic-, immunogenicity-, and magnetic resonance imaging-assessed alteration of vascular effects of IMC-1C11 were evaluated in this trial. IMC-1C11 was infused weekly at 0.2 mg/kg (n = 3), 0.6 mg/kg (n = 4), 2.0 mg/kg (n = 3), and 4.0 mg/kg (n = 4) for 4 wk, which constituted a cycle. No grade-3 or -4 IMC-1C11-related toxicities were obsd. Minor grade-1 bleeding events were obsd. in four patients [0.2 mg/kg (n = 1) and 0.6 mg/kg (n = 3)]. Each resolved quickly and required no intervention. The starting dose of IMC-1C11 was selected to achieve a Cmax of .apprx.5 .mu.g/mL. This concn. prevented KDR phosphorylation in vitro. Pharmacokinetic anal. demonstrated that the plasma t<sub>1/2</sub> and Cmax were dose dependent with a plasma t<sub>1/2</sub> of 67 +- 3 h at the 4-mg/kg dose level. Human anti-**chimeric** \*\*\*antibodies\*\*\* were detected in 7 of 14 patients. The antibodies to IMC-1C11 inhibited the circulation of the agent in two patients. One patient had prolonged stable disease for seven cycles (28 wk). The mean changes in tumor-influx vol.-transfer const. kin (min-1) and enhancement factor after 4 wk of therapy were significantly decreased compared with pretreatment values in 11 patients. IMC-1C11 was both safe and well tolerated. Drug levels of IMC-1C11 were reliably predicted. Further clin. investigation of anti-VEGFR/KDR agents is warranted.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2002:814159 CAPLUS  
DOCUMENT NUMBER: 137:336728  
TITLE: **Chimeric antibodies** and fragments or variants specific to vascular endothelial growth factor 2 for diagnosing, prognosing and treating infection, inflammation, cancer and autoimmune disease  
INVENTOR(S): Rosen, Craig A.; Albert, Vivian R.; Ruben, Steven M.; Wager, Ruth E.  
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA  
SOURCE: PCT Int. Appl., 407 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083704	A1	20021024	WO 2002-US11474	20020412
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 US 2003175274 A1 20030918 US 2002-120414 20020412  
 WO 2003097660 A1 20031127 WO 2002-US26246 20020819  
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
 CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
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 PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
 NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-283385P P 20010413  
                          US 2002-350366P P 20020124  
                          WO 2002-US11474 A 20020412

#### ABSTRACT:

Disclosed are anti-**VEGF-2** agonistic or antagonistic human or humanized antibodies, antibody fragments, or variants thereof. Also provided are processes for producing such antibodies. The present invention relates to methods and compns. for preventing, treating or ameliorating a disease or disorder comprising administering to an animal, preferably a human, an effective amt. of one or more **VEGF-2** antibodies or fragments or variants thereof. The disease is selected from inflammatory diseases, proliferative diseases, tumors, metastasis, breast cancer, brain cancer, prostate cancer, colon cancer, lymphangioma, infections, Kaposi's sarcoma, autoimmune diseases, rheumatoid arthritis, psoriasis, diabetic retinopathy, and other diseases assocd. with aberrant or lack of **VEGF-2** expression.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2002:709689 CAPLUS  
 DOCUMENT NUMBER: 137:211928  
 TITLE: Construction of eukaryotic expression system and its uses for antibody cloning  
 INVENTOR(S): Yang, Zhihua; Ran, Yuliang  
 PATENT ASSIGNEE(S): Inst. of Tumors, Tumor Hospital, Chinese Academy of Medical Sciences, Peop. Rep. China  
 SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 31 pp.  
 CODEN: CNXXEV  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Chinese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1328157	A	20011226	CN 2000-108065	20000609
PRIORITY APPLN. INFO.:			CN 2000-108065	20000609

#### ABSTRACT:

The invention relates to construction of plasmid vector for expression of antibody in eukaryote. The vector contains selective marker gene (such as aminoglycoside phosphate transferase, thymidine kinase, hygromycin B phosphate transferase, xanthine-guanine phosphoribosyltransferase, or asparagine synthase) and extensible selective marker gene (such as dihydrofolic acid reductase (dhfr) or glutamine synthase). The vector also contains weak promotor (such as 72 bp fragment-deleted SV40) for driving the expression of the said marker genes. The vector also contains strong promotor (such as PhCMV-IE, PSV40-E, or PRSV-LTR) for driving the expression of antibody gene.

The vector also contains enhancer sequence (such as 5'-non-translational region SP163 of mouse vascular endothelial growth factor). The vector further contains strong translation terminator (such as BGH polyA or SV40 polyA). The eukaryotic expression system is constructed by successively prep. general cloning vectors (such as pYR-GCVH and pYR-GCVL) of variable region of antibody, intermediate expression vectors (such as pYR-SV2-rdhfr and pYR-SV2-rneo) of antibody, and general eukaryotic expression vector (such as pYR-GSEVH, pYR-GSEVL, pYR-GCEVH, and pYR-GCEVL). The eukaryotic expression system is used to prep. and prodn. of antibodies (such as **chimeric antibody**, modified antibody, humanized antibody, small mol. antibody, intracellular antibody, double-specific antibody, and other derivs.). The **chimeric \*\*\*antibody\*\*\*** of human **VEGF** and small mol. antibody of human carcino-embryonic antigen (CEA) were prep'd. by using the eukaryotic expression system in CHO-dhfr- cell.

L3 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2002:695813 CAPLUS  
 DOCUMENT NUMBER: 137:231369  
 TITLE: Anti-VEGFR antibodies in combination with anti-EGFR antibodies, chemotherapeutic agent or radiotherapeutic agent for inhibiting tumor growth  
 PATENT ASSIGNEE(S): Imclone Systems Incorporated, USA; Rockwell, Patricia; Goldstein, Neil I.  
 SOURCE: PCT Int. Appl., 151 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 6  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070008	A1	20020912	WO 2002-US6762	20020304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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US 2003103973	A1	20030605	US 2001-798689	20010302
PRIORITY APPLN. INFO.:			US 2001-798689	A 20010302
			US 1994-196041	B2 19940210
			US 1994-326552	A1 19941020
			US 1995-476533	B2 19950607
			US 1996-706804	A2 19960903
			US 1997-967113	A1 19971110
			US 1999-401163	A2 19990922

#### ABSTRACT:

The present invention provides a method of reducing or inhibiting tumor growth in a mammal comprising treating the mammal with an effective amt. of a combination of a **VEGF** receptor antagonist and radiation, chemotherapy, and/or an addnl. receptor antagonist (e.g. epidermal growth factor receptor antagonist). The **VEGF** receptor antagonists are anti-VEGFR antibodies, fragments, humanized or **chimeric \*\*\*antibodies\*\*\***.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2002:409126 CAPLUS  
 DOCUMENT NUMBER: 137:5011  
 TITLE: Antibodies specific to human KDR VEGF  
 receptor for inhibiting angiogenesis and tumor growth  
 INVENTOR(S): Zhu, Zhenping; Witte, Larry  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 34 pp., Cont. of U.S. Ser. No.  
 493,539.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002064528	A1	20020530	US 2001-976787	20011012
PRIORITY APPLN. INFO.:			US 2000-493539	A1 20000128

ABSTRACT:

The invention provides an Ig. mol. which binds KDR with an affinity comparable to human VEGF, and that neutralizes activation of KDR. Ig. mols. include monovalent single chain antibodies, multivalent single chain antibodies, diabodies, triabodies, antibodies, humanized antibodies and \*\*\*chimeric\*\*\* antibodies. The invention further provides nucleic acid mols. that encode these Ig. mols. The invention also provides a method of making the Ig. mols. mentioned above. The invention further provides a method of neutralizing the activation of KDR, a method of inhibiting angiogenesis in a mammal and a method of inhibiting tumor growth in a mammal with such Ig. mols.

L3 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:338563 CAPLUS  
 DOCUMENT NUMBER: 134:348629  
 TITLE: Modulation of eNOS activity using VEGF, a variant, or VEGF receptor agonists and therapeutic uses thereof  
 INVENTOR(S): Shen, Ben-Quan; Zioncheck, Thomas  
 PATENT ASSIGNEE(S): Genentech, Inc., USA  
 SOURCE: PCT Int. Appl., 71 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032695	A2	20010510	WO 2000-US30294	20001102
WO 2001032695	A3	20020214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1225910	A2	20020731	EP 2000-980281	20001102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003513105	T2	20030408	JP 2001-535394	20001102
PRIORITY APPLN. INFO.:			US 1999-163132P	P 19991102
			WO 2000-US30294	W 20001102

**ABSTRACT:**

The present invention provides uses of **VEGF**, a variant, or \*\*\*VEGF\*\*\* receptor agonists for the up-regulation of eNOS expression and activity. **VEGF**, its variants, and **VEGF** receptor agonists are useful in the treatment of or prevention from hypertension, diabetes, angina, thrombosis, atherosclerosis, heart failure, and other conditions or disorders wherein nitric oxide is an important regulator. Methods of prep. the variants are also disclosed in the patent.

L3 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:911535 CAPLUS

DOCUMENT NUMBER: 134:85128

TITLE: Diagnostics and remedies for diseases with participation of macrocytes/macrophages

INVENTOR(S): Shitara, Kenya; Shibuya, Masabumi

PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan

SOURCE: PCT Int. Appl., 163 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

**PATENT INFORMATION:**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000079275	A1	20001228	WO 2000-JP3957	20000616
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1199565	A1	20020424	EP 2000-937283	20000616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRIORITY APPLN. INFO.:			JP 1999-171709	A 19990617
			WO 2000-JP3957	W 20000616

**ABSTRACT:**

Diagnostics and remedies for inflammatory diseases, delayed hypersensitivity, malignant tumor and arteriosclerosis which contain, as the active ingredient, a substance binding to human **VEGF** receptor Flt-1 or a substance inhibiting signal transduction mediated by human **VEGF** receptor Flt-1. The human **VEGF** receptor Flt-1-binding substance is a monoclonal or polyclonal antibody, **chimeric antibody**, or antibody fragment.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:219697 CAPLUS

DOCUMENT NUMBER: 133:118695

TITLE: Construction and expression of a chimeric murine-human antibody against VEGF165

AUTHOR(S): Guo, Wenzhong; Yang, Zhihua; Ran, Yuliang; Wang, Guiqi; Liu, Jun; Sun, Lixui; Dong, Zhiwei

CORPORATE SOURCE: Cancer Inst., Chinese Acad. Med. Sci., Beijing, 100021, Peop. Rep. China

SOURCE: Zhonghua Weishengwuxue He Mianyxixue Zazhi (2000), 20(1), 45-48

CODEN: ZWMZDP; ISSN: 0254-5101  
PUBLISHER: Weishenbu Beijing Shengwu Zhipin Yanjiuso  
DOCUMENT TYPE: Journal  
LANGUAGE: Chinese  
ABSTRACT:  
Objective To construct a chimeric murine-human antibody against VEGF165.  
Methods The murine genes encoding the variable regions of light and heavy chains of monoclonal antibody VmD11 against VEGF165 were cloned into expressional vectors of pAcyc-neo-C.kappa. and psv2-gpt-C.gamma.1 sep. The resulted vectors were transferred into murine-myeloma-cells to express \*\*\*chimeric\*\*\* antibodies. The chimeric antibody in the cultural supernatant of transfected cells was detected by indirect ELISA and its humanized character and specificity against VEGF165 was confirmed by Western blot, RT-PCR and competitive ELISA. Results The chimeric antibody against human VEGF165 was detected in the cultural supernatant of transfected myeloma cells with a yield of 10.mu.g/L. Specificity of the chimeric antibody was proved by Western blot and competitive ELISA, the expression of chimeric gene was confirmed by RT-PCR. Conclusion Chimeric mouse-human antibody against VEGF165 was successfully expressed in myeloma cells of mouse.

L3 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2000:7095 CAPLUS  
DOCUMENT NUMBER: 132:320697  
TITLE: Construction of anti-human VEGF165 chimeric antibodies and expression in eukaryotic cells  
AUTHOR(S): Ran, Yuliang; Yang, Zhihua; Wang, Guiqi; Liu, Jun; Sun, Lixin; Dong, Zhiwei  
CORPORATE SOURCE: Cancer Institute (Hospital), Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, 100021, Peop. Rep. China  
SOURCE: Zhonghua Zhongliu Zazhi (1999), 21(6), 412-415  
PUBLISHER: Zhongguo Yixue Kexueyuan Zhongliu Yanjiuso, Zhongliu Yiyuan  
DOCUMENT TYPE: Journal  
LANGUAGE: Chinese  
ABSTRACT:  
The chimeric anti-vascular endothelial growth factor 165 antibody gene was expressed in eukaryotic cells. The variable region genes of light and heavy chains from mouse anti-human VEGF165 monoclonal antibody VmD11 were cloned into eukaryotic expression vectors and transfected into dihydrofolated reductase-deficient Chinese hamster ovary (CHO-dhfr-) cells to express \*\*\*chimeric\*\*\* antibody. The antibody expressed was examd. for the presence of human const. regions and specificity against human VEGF165. The chimeric antibody with human const. regions and specificity against human VEGF was detected in the culture supernatant of transfected CHO cells by ELISA and Western blot. The chimeric antibody gene was also detected at mRNA level by RT-PCR. The mouse anti-human VEGF165 monoclonal antibody is successfully humanized and expressed in eukaryotic cells.

L3 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 1995:826808 CAPLUS  
DOCUMENT NUMBER: 123:225950  
TITLE: Monoclonal antibodies specific to VEGF receptors and uses thereof  
INVENTOR(S): Rockwell, Patricia; Goldstein, Neil I.  
PATENT ASSIGNEE(S): Imclone Systems Incorp., USA  
SOURCE: PCT Int. Appl., 67 pp.  
DOCUMENT TYPE: Patent

LANGUAGE: English

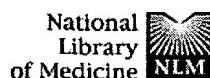
FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9521868	A1	19950817	WO 1995-US1678	19950210
W: AU, CA, CN, FI, HU, JP, KR, NO, RU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5840301	A	19981124	US 1994-326552	19941020
AU 9519147	A1	19950829	AU 1995-19147	19950210
EP 741748	A1	19961113	EP 1995-911659	19950210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
PRIORITY APPLN. INFO.:			US 1994-196041	A 19940210
			US 1994-326552	A 19941020
			WO 1995-US1678	W 19950210

ABSTRACT:

Monoclonal antibodies that specifically bind to an extracellular domain mammalian or human vascular endothelial growth factor (**VEGF**) receptor and neutralize activation of the receptor in endothelial or tumor cells are provided. The monoclonal antibodies are used in combination with a chemotherapeutic agent, e.g. doxorubicin, cisplatin, or taxol, for inhibition of tumor growth or angiogenesis. **Chimeric antibodies** comprising murine variable region and human const. region, polypeptides contg. the variable region of the monoclonal antibody, and nucleic acid sequences encoding the polypeptide are all claimed.



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- Search numbers may not be continuous; all searches are represented.

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#15	Search VEGF flt-1 and chimeric	14:25:11	22
#14	Search VEGF flt-1	14:19:35	863
#10	Search Rockwell P and VEGF	14:15:21	9
#7	Search Wang M and MSP	13:41:04	24
#6	Search Wang M	13:40:55	3085
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#3	Search Ssalvetti A 1998 and AAV	10:32:27	108
#1	Search Zhou X 1998 and AAV	10:31:04	1

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	#14 Search scFVs and VEGF	12:12:10	<u>3</u>
	#2 Search VEGF neutralizing antibody and cancer treatment	11:57:15	<u>56</u>
	#6 Search Rosenberg SA[au] Limits: Clinical Trial	11:27:00	<u>114</u>
	#4 Search VEGF neutralizing antibody and cancer treatment Field: All Fields, Limits: Clinical Trial	11:11:24	<u>3</u>
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1: Hybridoma. 1995 Oct;14(5):475-80.

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## Isolation and characterization of neutralizing monoclonal antibodies to human vascular endothelial growth factor/vascular permeability factor121 (VEGF/VPF121).

**Asano M, Yukita A, Matsumoto T, Matsuo K, Kondo S, Suzuki H.**

Bioscience Research Department, Tsukuba Research Laboratory, Toagosei Co. Ltd., Ibaraki, Japan.

We have established monoclonal antibodies (MAbs) against human vascular endothelial growth factor/vascular permeability factor121 (VEGF/VPF121). Two (MV101 and MV303) of the 28 MAbs neutralized the mitogenic activity of VEGF/VPF121 on human umbilical vein endothelial cells (HUVEC) in a dose-dependent manner. Both of the MAbs reacted to VEGF/VPF121 and also VEGF/VPF165 with somewhat different binding properties in a sandwich-type enzyme-linked immunosorbent assay (ELISA). The binding of MV101 and MV303 to VEGF/VPF121 was competitive, but MV415, another anti-VEGF/VPF121 MAb without neutralizing activity, did not compete with either of the antibodies. MV101 and MV303 specifically recognized the native form of VEGF/VPF121 and VEGF/VPF165 in Western blotting. They did not react with VEGF/VPF when the antigens were fractionated under reducing conditions. These observations suggested that MV101 and MV303 might recognize the epitopes closely located on the configuration of VEGF/VPF121 molecule and the epitopes recognized by MV101 and MV303 may play an important role in the VEGF/VPF-receptor signal transduction. These MAbs significantly suppressed the growth of a human hepatoma, PLC/PRF/5, in vivo.

PMID: 8575796 [PubMed - indexed for MEDLINE]

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□ 1: J Urol. 1999 Mar;161(3):960-3.

Related Articles, Links

**Neutralizing anti-vascular endothelial growth factor antibody inhibits further growth of established prostate cancer and metastases in a pre-clinical model.****Melnyk O, Zimmerman M, Kim KJ, Shuman M.**

Cancer Research Institute, University of California at San Francisco, USA.

**PURPOSE:** The formation of new blood vessels from the pre-existing vasculature is necessary for support of primary tumor growth and appears coincident with the development of metastasis. In previous studies, inhibition of vascular endothelial growth factor (VEGF), a potent angiogenic factor and mediator of vascular permeability, inhibited tumor neovascularization with consequent inhibition of both primary tumor growth and micrometastases when administered at the time of tumor inoculation. In the present study, we examined the effect of inhibiting VEGF on primary tumor growth and metastases in an *in vivo* model of established metastatic prostate cancer. **MATERIALS AND METHODS:** The human prostate cancer cell line DU-145 was found to secrete VEGF. DU-145.luciferase, a subclone stably transfected with an expression vector encoding the luciferase gene, injected subcutaneously, consistently formed tumors in C.B.-17 scid/scid mice. After 6 weeks, assay of whole lung lysates showed significant luciferase activity, consistent with the presence of micrometastasis. **RESULTS:** Twice weekly treatment of the animals with a monoclonal anti-VEGF neutralizing antibody, A4.6.1, not only suppressed primary tumor growth, but inhibited metastatic dissemination to the lung. When treatment was delayed until the primary tumors were well-established, further growth was still inhibited, as was the progression of metastatic disease. **CONCLUSION:** Inhibition of tumor-secreted VEGF by a neutralizing antibody is sufficient to significantly impair prostate tumor growth and its subsequent metastasis in an *in vivo* model of established advanced prostate cancer. These data suggest a critical role for VEGF in initiation and maintenance of tumor angiogenesis in prostate cancer. Inhibition of VEGF in patients with VEGF-secreting prostate cancers may prove an effective approach for inhibiting disease progression even after micro-metastatic dissemination has occurred.

PMID: 10022734 [PubMed - indexed for MEDLINE]



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1: Hum Gene Ther. 1996 Nov 10;7(17):2157-64.

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## Retroviral display of antibody fragments; interdomain spacing strongly influences vector infectivity.

**Ager S, Nilson BH, Morling FJ, Peng KW, Cosset FL, Russell SJ.**

Cambridge Centre for Protein Engineering, England.

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Five different single-chain antibody fragments (scFv) against human cell-surface antigens were displayed on murine ecotropic retroviral vectors by fusing them to the Moloney SU envelope glycoprotein. The spacing between the scFv and the SU glycoprotein was varied by fusing the scFv to residue +7 or to residue +1 of Moloney SU and by inserting linker sequences of different lengths between the domains. All of the chimeric envelopes were efficiently incorporated into vector particles and could bind to human cells through their displayed antibody fragments, but did not infect them. The spacing between the scFvs and the SU glycoproteins had no significant effect on the efficiency of envelope expression or viral incorporation and did not affect the binding properties of the chimeric envelopes, nor did it influence the efficiency of targeted gene delivery to human cells by scFv-displaying vectors. However, on murine fibroblasts the infectivity of vectors incorporating the chimeric envelopes was strongly influenced by the length of the interdomain spacer. The titers were very low when the single-chain antibodies were fused through a tripeptide linker to SU residue +7 and were greatly enhanced (up to 10(5)-fold) when they were fused to SU residue +1 through a heptapeptide linker. These results point to the importance of steric interactions between the domains of chimeric envelope glycoproteins and may have implications for retroviral vector design for human gene therapy.

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## Halting angiogenesis suppresses carcinoma cell invasion.

**Skobe M, Rockwell P, Goldstein N, Vosseler S, Fusenig NE.**

Division of Carcinogenesis and Differentiation, German Cancer Research Center (DKFZ), Heidelberg.

The importance of angiogenesis in malignant tumor growth has been interpreted mainly in terms of oxygen and nutrient supply. Here we demonstrate its fundamental role for tumor invasion of malignant human keratinocytes in surface transplants on nude mice. Distinct patterns of angiogenesis and vascular endothelial growth factor receptor-2 (VEGFR-2) expression allowed us to distinguish between benign and malignant cells. Functional inactivation of VEGF-R2 by a blocking antibody disrupted ongoing angiogenesis and prevented invasion of malignant cells, without reducing tumor cell proliferation. The reversion of a malignant into a benign phenotype by halting angiogenesis demonstrates a significant function of vascular endothelium for tumor invasion.

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# Anti-VEGFR-2 scFvs for Cell Isolation. Single-Chain Antibodies Recognizing the Human Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2/flk-1) on the Surface of Primary Endothelial Cells and Preselected CD34<sup>+</sup> Cells from Cord Blood

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**Key Words:** Immune V-gene phage display library· Single-chain antibody· Human VEGF receptor 2· FACS analysis· Hematopoietic stem cell

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## ► ABSTRACT

Five specific single-chain antibodies recognizing the human vascular endothelial growth factor receptor-2 (VEGFR-2/KDR) were selected from a V-gene phage display library constructed from mice immunized with the extracellular domain of VEGFR-2 (Ig-like domain 1-7). All five scFv antibodies (A2, A7, B11, G3, and H1) bound to the purified native antigen in enzyme-linked immunosorbent assay and Dot Blot, and showed no crossreactivity to the human VEGF-receptor 1 (VEGFR-1). The selected antibodies recognize a conformation-dependent epitope of the native receptor and do not recognize

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